ORIGINAL ARTICLE

Evaluation of the Relationship Between Neonatal Jaundice and Neurodevelopmental Delay in Full-Term Infants

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ABSTRACT

Introduction: In neonate's hyperbilirubinemia is a regular problem, in majority of the instances it is a benign condition. The unconjugated, non-polar, lipid soluble pigment accumulating in the skin results in yellow coloration. Normal bilirubin levels act as an antioxidant but it becomes a neurotoxic agent once its levels increase. The neurotoxic effects alter the permeability of the blood brain barrier and neuronal cell membranes, in addition increases the susceptibility of neurons to injury. The prodigious resilience from the neurotoxic effect have been overcome by a process of neuroplasticity created scope to evaluate the relation between neonatal jaundice and neuroplasticity . The present study is aimed at evaluating the relationship between neonatal jaundice and developmental delay. **Method:** A total of 103 neonates with neonatal jaundice were tested with standard scale Developmental Screening Test (DST) after 90 days to identify the developmental delays. **Results:** Out of 103 cases, 56 (54.36%) were male and 47 (45.64%) were female. A total of 24 (23.3%) cases showed positive neurodevelopmental delay in one or more than one domain and 79 (76.7%) infants were normal. Out of 24 neurodevelopmental delay cases, 16 cases (66.66%) were positive for single domain, 8 cases showed the neurodevelopmental delay in more than one domain constituting 33.33%. **Conclusion:** The results indicate a positive relation between neonatal jaundice and developmental delay. This provides a platform to carry out further research in the field to establish therapeutic approach.
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Keywords: Developmental Screening Test, Early intervention, Hyperbilirubinemia, Neonatal jaundice, Neuroplasticity.

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INTRODUCTION

The skin of the newborn acquires a yellowish color which is a clinical sign of jaundice due to the accumulation of bilirubin, known as hyperbilirubinemia. The yellow pigment bilirubin is found in the human body due to the recycling phase of the aging red blood cells. One of the most causes for readmission to the hospital after discharge is because of the jaundice which accounts for about 50% in full-term infants and 80% in premature infants during their first week of life (1). Bilirubin can be deposited in the brain as high levels can cross the blood-brain barrier, resulting in the development of kernicterus. This is the chronic form of bilirubin encephalopathy and can also lead to cerebral palsy, hearing loss and failure of upward gaze (2). The exact level of bilirubin that is neurotoxic is unclear, and it is not known what bilirubin levels are related to each neurodevelopmental disorder. Hyperbilirubinemia in newborns is detected by measuring unconjugated or free bilirubin (3) and although it may be having a physiological role as an antioxidant, high levels are neurotoxic (4-5). Normal levels of bilirubin in the blood range from 5-7 mg/dL and above this level result in the yellow coloration of the skin of the newborn. Neonates having blood bilirubin levels of 17 mg/dL account for five percent, and only 1.2% of this reach 20 mg/dL (6). For premature and full-term newborns accumulation of higher bilirubin levels are a neurological risk factor, like other factors such as birth weight, premature birth, intrauterine growth retardation, perinatal asphyxia, bronchopulmonary dysplasia, neonatal hypoglycemia and intraventricular hemorrhage (7-8). Further, higher bilirubin levels

augment the presence of other risk factors such as low birth weight or low gestational age (3,5), resulting in the increased risk of neurological damage in the premature newborn. Basal ganglia, hippocampus and cerebellum are the regions of the brain to where unconjugated or free bilirubin can travel in the blood (2,9). Minor neurological modifications like auditory dysfunctions associated with language disorders (5,10-13), decreased intellectual function associated with alterations in executive functions (10,14-15), visual impairment (5,10- 11,16) and dental abnormalities (2,5,9) are the result of the chronic state of neurotoxic bilirubin levels. Moderate levels have been associated with minor neurological dysfunctions at 1 year of life in full-term children (17), also the possibility of developing certain pathologies that affect neurodevelopment, such as autism spectrum disorder (ASD) (4,10) or attention-deficit hyperactivity disorder (ADHD) (13) these are in addition to the neurological damage that high doses produce in the nervous system (3).

Blood transfusion and phototherapy in perinatal care has bestowed to the resolution of jaundice and hyperbilirubinemia, and it has also significantly decreased the incidence of kernicterus (3). Perinatal care, early evaluation and early intervention have been shown to reduce neurological damage (18-19) and minimize the relevant sequelae. Most of the available literature reports the effect of hyperbilirubinemia in aged children. With these facts in mind the present study is designed to find out the relationship between hyperbilirubinemia and neurodevelopmental delay in full-term newborns by evaluating at early age (90 days postnatal).

MATERIALS AND METHODS

This study was conducted in 143 full-term newborn infants delivered in District Hospital, Kondapur, Hyderabad, India. A predesigned, prevalidated questionnaire was used to record the patient's data. Validation was done by the experts from the pediatric department. The study includes all infants with hyperbilirubinemia and were admitted for treatment of neonatal jaundice. Infants with congenital anomalies, meningitis, sepsis, intracerebral hemorrhage, asphyxia, hypoglycemia, cholestasis, epilepsy, malnutrition, hypothyroidism, and Down syndrome were excluded from the study. As these conditions were considered as interfering factors and result in the negative development of the infant, were removed from the research study. Hyperbilirubinemia was managed by phototherapy and exchange transfusion according to the guidelines published by the American Academy of Pediatrics subcommittee in all cases. Bilirubin levels were recorded after clinical diagnosis of the jaundice was made along with all other diagnostic tests data and at the time of discharge, age, duration of the SNCU stay, treatment protocol, breast feeding methods were recorded. Weekly follow up was advised and carried out regularly.

On completion of 90 days of post-natal age 103 infants were evaluated for neurodevelopmental delay by Developmental Screening Test (DST) assessment. 40 infants were excluded from the study. This assessment was done in five domains: motor, hearing, speech sounds, social smile and vision. Infants having problem with any of the one domain or more than one is considered as with neurodevelopmental delay.

The study protocol was approved by the Institution Ethics Committee, District Hospital, Kondapur, Hyderabad, Telangana, India (Reference No: ECR/02/Inst/Ts/2023/DH, No: 01/Ethics/2023, Dated 25/08/2023) and informed consent was obtained from parents.

RESULTS

Out of 143 cases 103 cases were included in the study. 40 infants were excluded due to various reasons and not available for follow up. In total of 103 cases, 56 (54.36%) were male and 47 (45.64%) were female. The bilirubin levels range was from 10 mg/dL to 25 mg/dL (Table I).

Table I: **Sample size and gender wise distribution along with serum bilirubin levels.**

Total No. of Cases	No of cases evaluated	No. of male (%)	No. of female (%)	Range of serum bilirubin (mg/dL)
140	103	56 (54.36)	47 (45.64)	10 - 25

A total of 24 (23.3%) cases showed positive neurodevelopmental delay in one or more than one domain and 79 (76.7%) infants were normal in all developmental aspects. In all the 24 cases the bilirubin levels were more than 15 mg/dL. Among the neurodevelopmental delay cases, males constituted 54.17% (n=13) and females were 45.83% (n=11) (Fig 1). Out of 24 neurodevelopmental delay cases, 16 cases (66.66%) were positive for single domain. Among 16 cases, 7 (29.17%) showed motor delay, 2 (8.33%) were having visual delay, 6 (25%) cases presented with hearing (speech sounds) delay and 1 (4.17%) case was social smile delay. Further, 8 cases showed the neurodevelopmental delay in more than one domain constituting 33.33% (Fig 2).

DISCUSSION

The amount of bilirubin when exceeds the albumin-binding capacity, it may result in neuronal injury after the passage of bilirubin through blood brain barrier and its conjugation to the brain phospholipid membrane (20). There are reports which are contradictory regarding the effects of hyperbilirubinemia on infant neurodevelopmental delay (20-22). So, this study attempted to explore the relation between neonatal

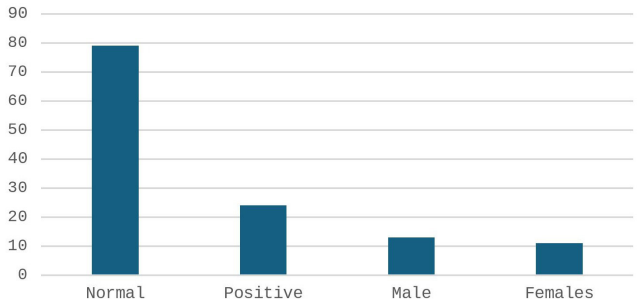

Figure 1: Normal, positive cases and gender distribution of neurodevelopmental delay cases in full-term newborn infants with neonatal jaundice at postnatal 90 days of age

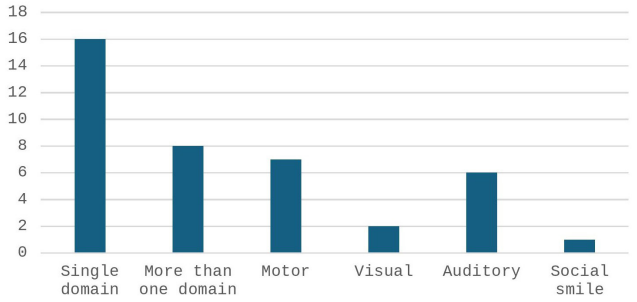

Figure 2: Domain distribution of neurodevelopmental delay cases in full-term newborn infants with neonatal jaundice at postnatal 90 days of age

jaundice and neurodevelopmental delay especially at an early age of postnatal 90 days in fill-term newborn individuals. The present study indicates a positive relationship between neonatal jaundice and neurodevelopmental delay in infants assessed at the age of postnatal 90 days. In vitro studies have shown that neuron maturation, cell viability, dendritic and axonal arborization, axonal growth cone morphology, dendritic spine formation, and synapse establishment are impaired by the higher bilirubin levels (23-24).

The results of the present study are similar to the earlier studies (25-27). In the present study auditory delay was found in 25% of cases which correlates with the study of W. Chen et al., (28). Ross reported that sensory development and motor control in full-term infants were affected by the moderately elevated levels of bilirubin (14). Dubey et al., reported motor abnormalities in full-term infants with high bilirubin levels (29). In the present study 29.17% cases showed single domain motor delay. Few of the earlier studies have reported bilirubin levels of more than 26 mg/dL, but we observed the neurodevelopmental delay in cases where bilirubin levels are above 15 mg/dL. This may be attributed to the different population groups. A study by Zhang et al., reported that there is a difference in neurodevelopmental damage which depends on age, pigment concentration level and the brain region where the deposition of the pigment takes place (30). In the present study the male infants are affected more than females. Amin et al., reported the potential effect on cognition due to hyperbilirubinemia in the population of full-term newborns could be related to the male (10). The strength of our study was the age of assessment of the infant which is postnatal 90 days. Most of the earlier studies have conducted the study at a later age, therefore our study results provide an opportunity for early assessment and implementation of early interventional therapy.

CONCLUSION

This study demonstrates a significant association between neonatal jaundice (hyperbilirubinemia) and early neurodevelopmental delay in full-term infants assessed at 90 days postnatally, with approximately one-quarter of infants showing delays, particularly in motor and auditory domains. Notably, developmental impairments were observed at bilirubin levels above 15 mg/dL, suggesting potential neurological risk even at moderate levels. These findings highlight the importance of early monitoring and developmental screening in jaundiced infants to enable timely intervention, leveraging early neuroplasticity to reduce long-term deficits. However, the relatively short follow-up period and absence of a control group limit causal inference. Future longitudinal studies with larger samples and extended follow-up are needed to clarify long-term outcomes and establish precise clinical thresholds.

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